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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,870	09/05/2003	George D. Purvis III	016939.0103 (03-52279-FAI)	7307
5073	7590	07/02/2008	EXAMINER	
BAKER BOTTS L.L.P. 2001 ROSS AVENUE SUITE 600 DALLAS, TX 75201-2980			BRUSCA, JOHN S	
			ART UNIT	PAPER NUMBER
			1631	
			NOTIFICATION DATE	DELIVERY MODE
			07/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ptomail1@bakerbotts.com
glenda.orrantia@bakerbotts.com

Office Action Summary	Application No. 10/655,870	Applicant(s) PURVIS, GEORGE D.	
	Examiner John S. Brusca	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,7,9-12,15,17,19-22,25,27 and 29-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,7,9-12,15,17,19-22,25,27 and 29-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

1. Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 are pending.

Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 are rejected.

Claim Rejections - 35 USC § 101

2. The rejection of claims 21, 22, 25, 27, 29, and 30 under 35 U.S.C. 101 for lack of statutory subject matter on the grounds that the claims read on a signal or carrier wave, and on the grounds that the claims read on a computer program per se or a scientific paper are withdrawn in view of the amendment filed 24 April 2008. The amendment requires a new grounds of rejection for new matter. The applicants may resolve this series of rejections by deletion of the new matter, retention of the limitation to software, and presenting a statement that the claims are limited to embodiments of computer readable media that are conventional in the art and do not encompass embodiments of software that are not physical embodiments of computer readable media.

3. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 are drawn to a process and apparatus and logic for executing the process. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank &

Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

The question of whether a claim encompasses statutory subject matter should not focus on *which* of the four categories of subject matter a claim is directed to 9-- process, machine, manufacture, or composition of matter--but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. See *In re Warmerdam*, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 do not require production of a tangible result in a form that is useful to the user of the process or apparatus. The claims recite a step of communication of the PMF score for presentation to a user without explicitly reciting a step of outputting a result in a form that is understandable to a user. The recited communication step could be storage of data in a computer memory in a form that is not interpretable to a user. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21, 22, 25, 27, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite the limitation "computer readable tangible media." The specification at the time of filing did not describe any form of computer readable media.

7. The rejection of claims 1, 2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention in the Office action mailed 17 December 2007 is withdrawn in view of the amendment and arguments presented by the applicants in their response filed 24 April 2008.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 11, 21, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Muegge et al. (Muegge I) (J. Med. Chem. Vol. 42, pages 2498-2503 (1999), reference G in the IDS filed 07 April 2004)

The claims are drawn to methods and apparatus therefor for computing a potential of mean force (PMF) score of a protein-ligand complex by determining the PMF of each atom pair of the complex. The method comprises calculation of a repulsion term for each atom pair analyzed.

Muegge I shows especially on page 2499 a method and apparatus for calculation of a PMF of a protein ligand complex by determining the PMF of each atom pair of the complex. Muegge I shows on page 2499 that consideration of the van der Waals interactions at short distances is beneficial for determination of the PMF of an atom pair because without such corrections for the short distance repulsion of van der Waals interactions the PMF would be infinity at short distances. Muegge I shows that if the van der Waals term is larger than 4 kcal/mol, the PMF is overwritten by the van der Waals term value.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge et al. (Muegge I) (J. Med. Chem. Vol. 42, pages 2498-2503 (1999), reference G in the IDS filed 07 April 2004) in view of Mitchell et al. (J. Comput. Chem. Vol. 20, pages 1165-1176 (1999), reference U in the notice of references cited mailed 07 March 2006).

The claims are drawn to methods and apparatus therefor for computing a potential of mean force (PMF) score of a protein-ligand complex by determining the PMF of each atom pair of the complex. The method comprises calculation of a repulsion term for each atom pair analyzed. In some embodiments sets of empirical data are used to derive the PMF of an atom pair. In some embodiments the empirical data that best agrees with data of the protein ligand complex is used.

Muegge I shows especially on page 2499 a method and apparatus for calculation of a PMF of a protein ligand complex by determining the PMF of each atom pair of the complex. Muegge I shows on page 2499 that consideration of the van der Waals interactions at short distances is beneficial for determination of the PMF of an atom pair because without such corrections for the short distance repulsion of van der Waals interactions the PMF would be

infinity at short distances. Muegge I shows that if the van der Waals term is larger than 4 kcal/mol, the PMF is overwritten by the van der Waals term value.

Muegge I does not show explicitly sets of empirical data used to derive the PMF of an atom pair or use of empirical data that best agrees with data of the protein ligand complex is used.

Mitchell et al. shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Mitchell et al. shows use of data from the Brookhaven Protein Databank on page 1167, and throughout to aid in determining PMF of atom pairs of interest.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the empirical data of Mitchell et al. to aid in determining the PMF values of Muegge I because Mitchell et al. shows use of empirical data in determining PMF values. It would have been further obvious to use empirical data that best agreed with the protein ligand under examination to improve accuracy of the method.

12. Claims 1, 2, 5, 7, 11, 12, 15, 17, 21, 22, 25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge I in view of Mitchell et al. as applied to claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 above, and further in view of Muegge et al. (Muegge II) (Med. Chem. Res. Vol. 9, pages 490-500 (1999), reference F in the IDS filed 07 April 2004).

The claims are drawn to a method and apparatus of determining a PMF score for a protein ligand complex in which the extent of agreement between root mean square values of the protein ligand complex and other structures used to predict the PMF scores of atom pairs of the protein ligand complex is a parameter of the quality of the PMF score.

Muegge I in view of Mitchell et al. as applied to claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 above does not show comparison of root mean square values of a protein ligand complex and structures used to determine a PMF of atom pairs of the protein ligand complex.

Muegge II shows in the abstract and throughout a method and apparatus for calculation of a PMF score of a protein ligand complex by determining the PMF of each atom pair of the complex. Muegge II shows comparison of root mean square deviations of multiple ligands on pages 492- 497.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Muegge I in view of Mitchell et al. as applied to claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 above by consideration of the root mean square deviations of data used in the method of Muegge II to improve accuracy.

13. Claims 1, 2, 5, 9, 10, 11, 12, 15, 19, 20, 21, 22, 25, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muegge I in view of Mitchell et al. as applied to claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 above, and further in view of Morris et al. (J. Comput. Chem. Vol. 19, pages 1639-1662 (1998), cited as reference L in the IDS filed 07 April 2004).

The claims are drawn to a method and apparatus of determining a PMF score for a protein ligand complex in which data used to generate a PMF of atom pairs in the complex is determined by a genetic algorithm.

Muegge I in view of Mitchell et al. as applied to claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 above does not show data used to generate a PMF of atom pairs in the complex determined by a genetic algorithm.

Morris et al. discloses methods of using genetic algorithms in docking programs to predict bound conformations of flexible ligands. Morris et al discuss the known methods of 3 dimensional protein-ligand analysis, which include the automated determination of minimized free energy conformations. Morris discusses known genetic algorithms (1641), and their use in docking programs. The genetic algorithm is used for searching the global computational space to identify a most fit structure of the protein-ligand interaction. The AUTODOCK program performs a specified number of dockings, then carries out conformational cluster analysis on the docked conformations to determine which are similar ranked by increasing energy. The “fitness” of the structure can be based on a variety of parameters. AUTODOCK uses a dispersion/repulsion term, a hydrogen bonding term, and a screened Coulombic electrostatic potential. MSMS is used to compute the analytical molecular surfaces, which discuss appears analogous to a well-depth value. Morris found their combination of the genetic algorithm with the free energy calculations and docking/design programs to provide faster and more reliable results.

It would have been prima facie obvious to one of ordinary skill in the art to apply the known computation methods of genetic algorithms to the methods of Muegge I in view of Mitchell et al. as applied to claims 1, 2, 5, 9, 11, 12, 15, 19, 21, 22, 25, and 29 above for scoring PMF functions of protein-ligand interactions as they provide faster and more successful searching of free energy conformations as shown by Morris et al.

Response to Arguments

14. Applicant's arguments filed 24 April 2008 have been fully considered but they are not persuasive. The applicants state that Muegge I does not show determination of a well depth value

of an atom pair, however the specification defines well depth value broadly on page 7, lines 27-28 as an amount of binding interaction between the two atoms in the protein-ligand pair. The determination of van der Waals interactions shown by Muegge I is a type of well depth value, and the argument is not persuasive. The applicants state that Muegge I teaches away from Mitchell et al. because Muegge I precomputes a PMF score for a protein at page 2499, while Mitchell et al. computes PMF for each atom pair. However Muegge I shows in formula 1 on page 2499 that the PMF is determined by a summation of each protein ligand atom pair value. The discussion of precomputation of protein s on a fixed grin in column 2 of page 2499 of Muegge I refers to implementation of a PMF score determined by equation 1 into the COCK4 program rather than teaching away from the use of equation 1.

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John S. Brusca/
Primary Examiner
Art Unit 1631

jsb